Claim 44 (original): The method according to claim 35 or claim 36, wherein the neuroprotection is for ischemic stroke or acute ischemic stroke.

Claim 45 (original): The method according to claim 35 or claim 36, wherein the neurons having high intracellular calcium concentration are preischemic and/or ischemic neurons.

Claims 46-65 (withdrawn)

REMARKS

Status of the Claims

Claims 1-65 are pending in the application. Claims 1-45 are rejected.

In this Amendment, claims 46-65 have been withdrawn without prejudice or disclaimer to comply with the restriction/election requirement for the application, and to expedite the patent application process. Applicants reserve the right to present these claims and the cancelled subject matter in a continuing application.

Rejection Under 35 USC §112, First Paragraph

Claims 1-8, 12-15, 19-23, 28-37, 41, and 43-45 have been rejected under 35 U.S.C. §112, first paragraph, as lacking enablement. Specifically, the Examiner states that the specification, "while being enabling for the specific fluoro-oxindole and chloro-oxindole compounds disclosed...does not reasonably provide enablement for all maxi-K potassium channel openers known to man at present or those which may be discovered in the future." The rejections under 35 U.S.C. §112, first paragraph, are respectfully traversed. In the Office Action, the Examiner states:

> The instant specification does not give any guidance as to the full range of openers of maxi-K potassium channels that could be used to treat a disease or disorder using the instant claimed process. In order to practice the claimed invention, one skilled in the art would

> have to speculate which compounds could be used to treat a disease or disorder found in the instant claims. The number of possible compounds that could be embraced by the claims that would have to be tested would impose undue experimentation on the skilled art worker.

According to this reasoning, the Examiner argues that "the broad terminology 'an opener of maxi-K potassium channels' is not enabled because the metes and bounds of compounds that could be used to treat a disease or disorder in the instant claims cannot be ascertained." It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. In re Angstadt, 537 F.2d 498, 502-03, 190 U.S.P.Q. (BNA) 214, 218 (CCPA 1976). However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly at it is claimed. In re Vaeck, 947 F.2d 488, 496, 20 USPQ 2D 1438 (Fed. Cir. 1991). Applicant asserts that the specification enables one skilled in the art to identify those compounds falling within the scope of the claims without undue experimentation. In fact, the specification provides specific guidance that enables the skilled artisan to identify maxi-K channel openers that are selectively efficacious in cells having condition of high intracellular calcium through routine experimentation. Applicant draws the Examiner's attention to the section of the application entitled "Screening Assays and Methods" (page 18, lines 15-page 18, line 2). As taught in that section, "[a]n embodiment of the present invention involves assays and methods for identifying, detecting, or screening for maxi-K opener compounds that function to open these types of potassium channels in cells having high levels of intracellular calcium, while not having significant opening activity on maxi-K channels in cells having low or normal levels of intracellular calcium" (page 18, lines 16-21).

The application teaches that "[o]ne such method involves testing a candidate opener compound in a cell-based assay under controlled intracellular calcium conditions" (page 18, lines 30-32). The screening procedure taught in the application employs cells having high intracellular calcium concentration and cells having low, moderate, or physiologically normal intracellular calcium concentration (page 19, lines 6-10). The application teaches that standard

patch-clamp analyses and recording techniques can be performed to determine if maxi-K channel outward currents are increased or activated after introduction of the candidate or test compound at high $[Ca^{2+}]_i$, compared with the effects of the candidate or test compounds on maxi-K channel outward currents at low or normal $[Ca^{2+}]_i$ (page 19, lines 11-23). Further, if "a candidate or test compound is determined to function as a Ca^{2+}-senitive and selective opener of maxi-K channels according to the present invention, it will cause the I-V [current-voltage] relationships of the whole-cell currents mediated by the maxi-K channel to shift to the left with increasing intracellular calcium concentration, while having no significant effect under low $[Ca^{2+}]_i$ conditions" (page 19, lines 23-28).

The application provides a specific example of the use of *Xenopus* oocytes which have been transduced with cloned maxi-K potassium channels (page 20, lines 7-10). In this embodiment, two-electrode voltage-clamp techniques could be employed to evaluate the response to a candidate by recording changes in the current voltage relationship (page 20, lines 12-15). As noted in the application, oocytes have low endogenous levels of intracellular calcium. Therefore, a test compound falling within the scope of the present invention does not significantly open the maxi-K channels in oocytes, but does open these channels in the maxi-K channel-expressing cells assayed under conditions of high levels of $[Ca^{2+}]_i$ (page 20, lines 16-22). The disclosed screening process is set forth in greater detail in working Examples 1 and 2 of the application.

Example 1 discloses a method for preparing HEK-293 cells transfected with a plasmid containing *hSlo* α-subunit cDNA (i.e., cDNA encoding maxi-K potassium channels). Example 1 provides a methodolgy (which is known in the art) for examining the outward K^+-mediated currents using standard whole-cell patch-clamp techniques (page 26, lines 30-32). Further, Example 1 discloses the preparation of bathing solutions of the fluoro-oxindole compound BMS-204352 and the chloro-oxindole compound BMS-225113 (page 27, lines 20-27).

Example 2 discloses an assay based on whole-cell voltage-clamp techniques. In this method, *hSlo*-mediated outward currents were recorded with pipettes containing different concentrations of Ca^{2+} (page 28, lines 1-4). Introduction of the test compounds BMS-204352

and BMS-225113 under the conditions described in Example 1 resulted in increased whole-cell *hSlo*-mediated outward currents in a concentration dependent and reversible manner (page 28, lines 7-10). However, these compounds produced significant increases in *hSlo*-mediated outward currents only at the highest concentrations of calcium. Example 2 further provides extensive guidance for performing the outside-out and whole cell patch analyses according to the screening process of the present invention (page 29, line 25-page 30, line 26).

Example 12 illustrates the use of the disclosed screening technique to identify a compound that works according to the invention ("BMS-A"), as well as an inoperable compound ("NS-1619") that does not exhibit selective calcium dependent channel opening. NS-1619 is a benzimidazolone compound that is known in the art as an opener of potassium channels. The compounds were study using standard whole-cell patch clamp techniques in HEK-293 cells genetically engineered to express a human brain *hSlo* α-subunit. The whole-cell patch clamp data shown in Figure 5A, indicates that BMS-A increased *hSlo*-mediated current amplitudes at the highest voltages at $[Ca^{2+}]_i \cong 2.5$ μM – i.e. high levels of intracellular calcium. At low levels of intracellular calcium, $[Ca^{2+}]_i \cong 50$ nM current amplitudes are actually decrease over a wide range of voltages, thus identifying BMS-A as a selective opener of Maxi-K channels under conditions of high intracellular calcium. In contrast, Figure 5C illustrates that NS-1619 increases *hSlo*-mediated current amplitudes at both high and low concentrations of intracellular calcium. Accordingly, this Example demonstrates that the disclosed screening techniques effectively identifies the selective Maxi-K openers of the present invention, while eliminating Maxi-K openers that do not exhibit the required calcium-dependent selectivity.

Regarding the Examiner's contention that the "number of possible compounds that could be embraced by the claims that would have to be tested would impose undue experimentation on the skilled art worker," Applicant reminds the Examiner that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985); In re Wands, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) ("The test is not merely quantitative, since a considerable amount of

experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.").

Furthermore, one skilled in the art would recognize that the interaction between a maxi-K channel opener and the proteins comprising the maxi-K channel is governed by the same general principles of ligand-receptor interactions that are ubiquitous in the biological sciences. It is known in the art that such interactions are largely influenced by the steric environment of the receptor site and families of modulators specific to a particular receptor exhibit a large degree of structural similarity. Accordingly, the skilled artisan would identify compounds that share similar structural characteristics with the compounds disclosed in the present application as candidates for screening.

In light of the considerable direction and guidance provided in the instant specification for screening selective openers of maxi-K channels under elevated intracellular calcium concentration, the high level of skill in the art (i.e., a Ph.D. researcher), and the fact that the methods needed to perform the disclosed screening are all well known, Applicant submits that one skilled in the art can readily ascertain those compounds that fall within the scope of the present claims without undue experimentation.

Additionally, the Examiner contends that the "nature of the pharmaceutical arts is that is involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no obsolete predictability even in view of the seemingly high level of skill in the art." Applicant respectfully point out that there is no requirement of "absolute predictability." Rather, all that is required is a "reasonable correlation" between *in vitro* and *in vivo* models. see Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). The Examiner's attention is directed to Examples 7 and 8 of the present specification which provide extensive data regarding the efficacy of BMS-204352 in reducing the degree of cortical infarct following permanent focal occlusion of the proximal middle cerebral artery (MCA) in *in vivo* rat models. Applicant submits that, based on this evidence, one skilled in the art would accept the *in vitro* screening model as reasonable correlated to the condition (i.e.,

ischemic stroke) sought to be treated by the present invention. Further, the Examiner has present no reasons to support her conclusion that the "existence of these obstacles establishes that contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regiment on its face" as required by MPEP § 2164.02.

In view of the forgoing, withdrawal of the rejection under 35 U.S.C. §112 is respectfully requested.

Rejection Under 35 USC § 102(b)

Claims 1-10, 12-17, 19-26, 28-40, and 43-45 are rejected under 35 U.S.C. § 102(b) as being anticipated by the '483 and '169 patents. Specifically, the Examiner states that Example 14 of the '483 patent discloses "an opener of the large-conductance calcium-activated potassium channels (also known as maxi-K channels) and is useful in the treating of disorders (e.g., ischemic stroke, traumatic brain injury, etc.) which are responsive to the opening of the potassium channels..." Further, the Examiner states that Examples 14, 37 and 38 of the '169 patent disclose "openers of the large-conductance calcium-activated potassium channels and are useful in the treating of disorders (e.g., ischemic stroke, traumatic brain injury, etc.) which are responsive to the opening of the potassium channels..." The rejections under 35 U.S.C. §102(a) are respectfully traversed.

Briefly, Applicant's invention relates to novel maxi-K channel opener or activator compounds that increase the open probability of, and augment the function of, mammalian maxi-K channels (page 5, lines 2-4). The application teaches that modulation of these channels could provide a therapeutic option for protecting cells exposed to conditions of hyperexcitability or pathogenic levels of Ca^{2+} such as neuronal cells affected during stroke (page 3, lines 21, 24). In another aspect of the invention, methods are provided for the treatment or prevention of diseases in mammals, particularly humans, characterized by affecting cells having high levels of intracellular calcium in which maxi-K channel proteins are specifically targeted as a result of the high intracellular calcium concentration of the affected cells (page 6, lines 22-27). The application teaches non-limiting examples of such diseases, including stroke, global cerebral

ischemia, traumatic brain injury, Parkinson's disease, epilepsy, migraine and chronic neurodegenerative disorders such as Alzheimer's disease (page 6, lines 27-30). The openers according to the invention are sensitive to the intracellular calcium concentration of cells, and are demonstrated to be most effective under conditions of increased intracellular calcium concentrations, while being minimally effective, or not at all effective, under normal to low intracellular calcium concentrations (page 5, lines 4-9). The application teaches that other opener compounds have been shown to lack sensitivity to intracellular calcium concentration and thus their actions are independent of the concentration of intracellular calcium (page 4, lines 21-24). Method claims 1-45 each incorporate this novel aspect of the invention as explicit limitations. For instance, independent method claim 1 requires, *inter alia*, providing an effective amount of an opener of maxi-K channels which does not "significantly activate maxi-K potassium channels in cells under low or normal concentrations of intracellular calcium."

In contrast, the '483 and '169 patents do not teach calcium-dependent maxi-K channel openers which exhibit specific opening of these channels at high levels of intracellular calcium, but which have little effect on these channels in cells having low intracellular calcium levels. The '483 patent relates generally to novel substituted 3-phenyl oxindole derivatives which are modulators of the large-conductance calcium-activated potassium (Maxi-K) channels (col. 1, lines 6-9). The genus of substituted 3-phenyl oxindole derivatives according to the invention of the '483 patent is disclosed in Formula I (col. 2, lines 26-40). The '483 patent teaches that these compounds are useful in the protection of neuronal cells, especially in the treatment or prevention of ischemic stroke (page 2, lines 19-24). Further, the '483 patent discloses a method for the treatment of or protection from disorders which are mediated by the opening Maxi-K channels in a mammal in need of treatment comprising administering a therapeutically effective amount of a compound of Formula I (col. 13, lines 41-47). The disclosure of the '169 patent is nearly identical to the disclosure of the '483 patent[1]. However, there is no teaching in either the '483 or '169 patents of methods of treatment or compounds which selectively open maxi-K channels in cells having high intracellular calcium concentration while having no significant

[1] The '169 patent, which issued as a continuation-in-part from the application which issued as the '483 patent, adds to the disclosure Examples 37 and 38.

opener activity of maxi-K channels in cells having normal or low intracellular calcium concentration. Since neither the '483 nor '169 patent teach every limitation of claims 1-10, 12-17, 19-26, 28-40, and 43-45, applicant requests that the rejection under 35 U.S.C. § 102(b) be withdrawn.

Rejection Under 35 USC § 103(a)

Claim 1-45 are rejected under 35 U.S.C. § 103(a) as obvious over the '483 and '169 patents. Specifically, the Examiner states that the '483 and '169 patents "teach fluoro-oxindole compounds, which are openers of the large-conductance calcium-activated potassium channels (also known as maxi-K channels) and are useful in the treating of disorders (e.g., ischemic stroke, traumatic brain injury, etc.) which are responsive to the opening of the potassium channels..." Further, the Examiner argues that "[o]ne skilled in the art would thus be motivated to prepare products embraced by the Hewawasam et al. references, or alternatively, prepare the chloro-oxindole products instead of the fluoro-oxindole products, to arrive at the instant claimed invention with the expectation of obtaining products which would be useful in treating disorders such as stroke, traumatic brain injury, etc."

The rejections under 35 U.S.C. §103(a) are respectfully traversed. The Examiner argues that claims 1-45 are obvious over the disclosures of the '483 and '169 patents. Particularly, the Examiner characterizes the present invention as "a method of treating a disease or disorder characterized by high intracellular calcium levels comprising providing an effective amount of an opener of maxi-K potassium channels (e.g. fluoro-oxindole and chloro-oxindole compounds." Furthermore, the Examiner argues that the '483 and '169 patents teach "fluoro-oxindole compounds which are openers of the large-conductance calcium-activated potassium channels (also known as maxi-K channels) and are useful in the treating of disorders (e.g. ischemic stroke, traumatic brain injury, etc.) which are responsive to the opening of the potassium channels." Applicant respectfully submits that the Examiner has misconstrued the present invention insofar as the Examiner states that the subject matter of the present claims are *prima facie* obvious in light of the fluoro-oxindole openers disclosed in the '483 and '169 patents. As discussed above,

the subject matter of claims 1-45 relates to methods of treatment whereby compounds selectively open maxi-K channels in cells having high intracellular calcium concentration while having no significant opener activity of maxi-K channels in cells having normal or low intracellular calcium concentration. In contrast, there is no suggestion in either the '483 or '169 patents that the compounds disclosed therein have little or no effect on cells having normal or low intracellular calcium concentrations as required by instant claims 1-45.

Applicants submit that the '483 and '169 patents neither teach nor suggest Applicants' invention as embodied in claims 1, 14, 22, 35 and 36. Having distinguished the independent claims, Applicants do not here address the dependent claims but reserve the right to do so in the future should such become necessary.

Obviousness-Type Double Patenting

Claims 1-10, 12-17, 19-26, 28-37 and 43-45 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 23, 24 and 28-31 of the '483 patent and over claims 5-10 of the '169 patent. The Examiner states that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because there is an overlap between the subject matter in the instant claims and the subject matter embraced by the claims in the patents." Applicant submits that the present claims are patentably distinct from any claim of the '483 or '169 patents. While not admitting that the claims of the present application are obvious over any claim of the '169 or '483 patent, Applicant submits herewith a terminal disclaimer pursuant to 37 C.F.R. §1.321(c) for commonly owned U.S. Patent 5,565,483 and 5,602,169 in order to expedite the examination of this application. According, the obviousness-type double patenting rejection has been traversed.

CONCLUSION

For the above-stated reasons, this application is believed to be in condition for allowance. Applicants respectfully request an early and favorable examination on the merits.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for the timely consideration of this amendment under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account No. 19-3880. A duplicate of this page is herewith enclosed.

Respectfully submitted,

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